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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61J 3/07

A1

(11) International Publication Number: WO 00/28942

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/EP99/08684

(22) International Filing Date: 11 November 1999 (11.11.99)

(30) Priority Data:
98121831.6 17 November 1998 (17.11.98) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).

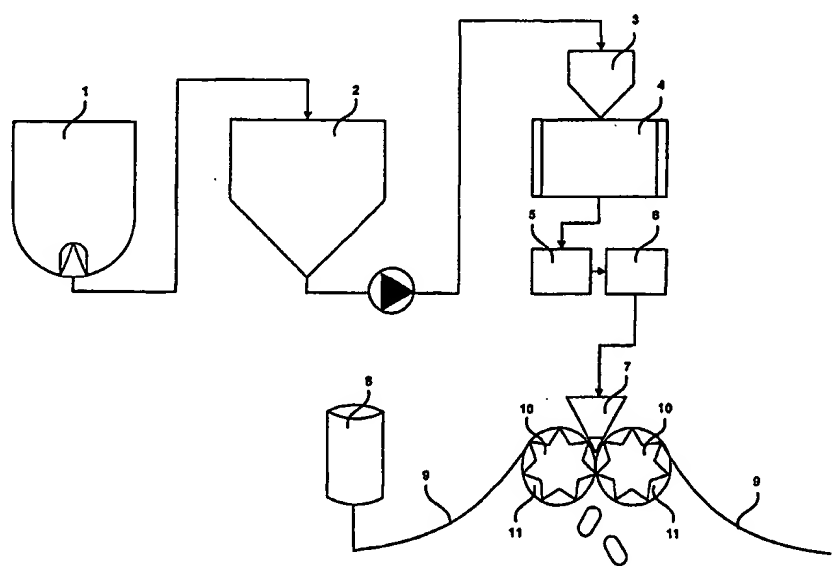
(72) Inventors: ALEX, Rainer; Bühlstrasse 45, D-79576 Weil am Rhein (DE). GERHARDS, Jürgen; Mühlebodenweg 1, CH-4144 Arlesheim (CH). KRAEMER-PITTROF, Ingeborg; Am Reinenbächle 3, D-79618 Rheinfelden (DE). OESCHGER, Richard; Langacherstrasse 22, CH-5084 Rheinsulz (CH). RADES, Thomas; 14 Elliot Street, Dunedin (NZ).

(74) Agent: WAECHTER, Dieter; Grenzacherstrasse 124, CH-4070 Basle (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROCESS FOR THE MANUFACTURE OF LIQUID FILLED CAPSULES



(57) Abstract

The present invention relates to a process for encapsulating a shear sensitive fill mass into a capsule, characterised in that said fill mass is heated and subsequently cooled, immediately prior to the encapsulation. The invention relates also to the capsules obtainable by the said process. The process according to the present invention enables to obtain capsules showing high and constant dissolution rates. The amount of active agent intake can be therefore reduced since the active agent itself is rapidly dissolved. The overall costs of the medicament are thereby also reduced. The high homogeneity (and therefore the high and constant dissolution rate) of the capsules produced with the process according to the present invention guarantees a reproducible bioavailability and therapeutic effect of the active agent which is contained in it.

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Process for the manufacture of liquid filled capsules

The present invention relates to a process for encapsulating shear sensitive fill masses into capsules and to the capsules obtainable by said process.

The term "capsule" encompasses hard and soft shell capsules which are preferably used to administer nutrients or pharmaceutically active ingredients to individuals. Such capsules are soluble under physiological conditions, digestible or permeable. The capsule shells are usually made of gelatin, starch, or other suitable physiologically acceptable macromolecular materials in form of gels.
Examples thereof are soft gelatin capsules, hart gelatin capsules and Hydroxy Propyl Methyl Cellulose (HPMC) capsules.

In particular, the present invention provides a process for encapsulating shear sensitive fill masses into gelatin capsules and to the gelatin capsules obtainable by said process.

Owing to their special properties and advantages, gelatin capsules are used widely in the pharmaceutical industry. They can be applied as an oral dosage form, as a suppository dosage form for rectal use or for vaginal use, as a speciality package in tube form, for human and veterinary single dose application, in the cosmetic industry etc. Their capsule shell is basically composed of gelatin and water; it may contain additional ingredients such as plasticisers, preservatives, colouring and opacifying agents, flavouring, sugars, acids, and medicaments to achieve desired effects.

Gelatin capsules can be used to dispense a variety of different active compounds. Several advantages of gelatin capsules derive from the fact that the drug may be a liquid or at least

dissolved, solubilised, or suspended in a liquid vehicle. Since the capsule fill mass is metered into individual capsules by a positive-displacement pump, a much higher degree of reproducibility is achieved than is possible with powder or granule feed in the manufacture of tablets and powder or granule filled hard gelatin capsule products. The biopharmaceutical availability of drugs formulated as liquid filled gelatin capsules, as measured by disintegration time or dissolution rate, often shows an advantage over other solid dosage forms. The biopharmaceutical characteristics of such formulations can be altered or adjusted more easily than those of other dosage forms. Through the selection and use of liquids and combinations of liquids that range from water immiscible through emulsifiable to completely water-miscible, and by altering the type or quantity of thickening or suspending agents, capsule formulations allow more flexibility in the design of a dosage form to fit biopharmaceutical specifications of a particular therapeutic agent. Suitable vehicles which can be used for preparing fill masses for encapsulation may be chosen among the aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, high-molecular-weight-alcohols, esters and organic acids, vegetable oils, mineral oil, silicon oil, non-ionic surface active agents, polyethylene glycols, medium chain triglycerides and medium chain mono and diglycerides, either alone or in combination.

Mainly, two different kinds of gelatin capsules are commonly used, i.e. soft and hard gelatin capsules.

Several processes are known in the art for producing soft gelatin capsules. The most important is the rotary die process, which is a continuous flow process developed by Scherer first in 1933 (J.P.Stanley, *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., 1986, p 398-412).

According to this process, the gelatin mass is fed by gravity to a metering device (spreader box), which controls the flow of the mass onto air-cooled rotating drums. Gelatin ribbons of controlled thickness are therefore formed. The ribbons are fed through a lubricating bath, over guide rolls, and then down between an injection wedge (for the fill material) and die rolls. The material to be capsulated, which is previously mixed and stored, flows by gravity into a positive displacement pump. The pump accurately meters the material through a leads and the wedge and into the gelatin ribbons between the die rolls. The capsule is about half sealed when the pressure of the pumped material forces the gelatin

into the die pockets, where the capsules are simultaneously filled, shaped, hermetically sealed and cut from the gelatin ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating of the ribbons by the wedge. All fill masses (e.g. liquids, solutions, and suspensions) for encapsulation should preferably flow at room temperature and in any case at a temperature not exceeding 35°C at the point of encapsulation, since the sealing temperature of the gelatin films must remain below this temperature.

Several types of filling machines for hard gelatin capsules are known in the pharmaceutical industry (Larry L. Augsburger, Hard and Soft Shell Capsules, Modern Pharmaceutics, G.S.Banker, C.T. Rhodes (Eds.), Third Edition, Marcel Dekker Inc. (1996), 395-428)

The liquid fill mass can be prepared as described for the soft gelatin capsules process. The empty capsules, comprising a cap and a body portion, are oriented so that all point in the same direction (i.e. body-end downward). In general the capsules pass one-at-time through a channel just wide enough to provide a frictional grip at the cap end. A specially designed blade pushes against the capsule and causes it to rotate about its cap end as a fulcrum. After two pushes (one horizontally and one vertically downward), the capsules will always be aligned body-end downward, regardless of which end entered the channel first. At this point the caps are separated from the bodies. Here, the rectified capsules are delivered body-end first into the upper portion of split bushings or split filling rings. A vacuum applied from below pulls the bodies down into the lower portion of the split bushing. The diameter of the caps is too large to allow them to follow the bodies into the lower bushing portion. The split bushings are then separated to expose the bodies for filling. The body portion of the capsule can be thus filled with the fill mass which cannot exceed a temperature of 60°C. The cap and body bushing portions are rejoined wherein pins are used to push the filled bodies up into the caps for closure, and to push the closed capsules out of the bushings. Compressed air also may be used to eject the capsules. If necessary, hard gelatin capsules may be made hermetically by e.g. banding (i.e. layering down a film of gelatin, often distinctively colored, around the seam of the cap and body).

Using the above mentioned processes, however, it has been unfortunately found that shear sensitive fill masses can totally or partially solidify before being encapsulated, or even in the capsules upon storage. The solidification of the fill mass or of one or more components

thereof is due to mechanical phenomena, such as the shear stress, which occurs at various points of the manufacturing process. The most critical parts of the plant are the mixing vessels and the pumps, wherein the shear stress dramatically increases with increasing viscosity of the fill mass.

This total or partial solidification can cause significant and unacceptable changes in the pharmaceutical quality of the product like, for example, reduction and variability of the capsules dissolution rate, and hence the bioavailability of the drug substance and the therapeutic effects of the drug.

The problem at the root of the present invention is therefore to provide a process for encapsulating shear sensitive fill masses into gelatin capsules which can overcome the above mentioned problems.

This problem is solved, according to the present invention, by a process for encapsulating a shear sensitive fill mass into a capsule, characterised in that said fill mass is heated and subsequently cooled, immediately prior to the encapsulation.

The solid component of the fill mass, which has formed due to shear stress during the mixing and pumping stages of the process, can be re-liquefied or re-dissolved by heating it. The temperature to which the fill mass must be heated depends on the physical and chemical characteristics of the fill mass itself.

Since the encapsulation temperature for soft and hard gelatin capsules should usually not exceed 35°C and 60°C, respectively, the homogeneous fill mass must be subsequently cooled to room temperature, and in any case below said temperatures. It has been surprisingly found that, once cooled, the homogeneous shear sensitive fill mass does not return into the original solid state as long as it does not undergo further mechanical strain. According to the present invention, the heating and subsequent cooling of the fill mass take place immediately prior to encapsulation so that the content of the obtained capsule remains homogeneous and limpid over the whole life time of the medicament. The heating and cooling of the fill mass can be carried out in conventional manners, e.g. by letting flow it through spiral tubes immersed in water/oil baths and cold water bath, respectively. As the contact time of the fill mass in the heating device can be varied by modifying the

residence time in the bath, heating of the fill mass after the dosing pump is also suitable for thermolabile substances.

The process according to the present invention enables to obtain gelatin capsules showing high and constant dissolution rates. The amount of active agent intake can be therefore reduced since the active agent itself is rapidly dissolved. The overall costs of the medicaments are thereby also reduced. The high homogeneity (and therefore the high and constant dissolution rate) of the gelatin capsules produced with the process according to the present invention guarantees a reproducible bioavailability and therapeutic effect of the active agent which is contained in it.

In the case the capsule is made of soft gelatin, the fill mass is preferably heated at a temperature between 0 and 20°C above its melting point, and subsequently cooled at a temperature between 35 and 20°C.

In the case hard gelatin capsules are produced, the fill mass is preferably heated at a temperature between 0 and 20°C above its melting point, and subsequently cooled at a temperature between 60 and 20°C.

The process according to the present invention is suitable for fill masses like, for instance, emulsions, dispersions and solutions comprising the pharmaceutically active agent(s), as well as for pure pharmaceutically active agents in the liquid state. Particularly, the process according to the present invention is suitable for fill masses comprising high doses of a sparingly soluble pharmaceutical agent such as e.g. a HIV protease inhibitor and, more particularly, for solutions of saquinavir. These particular fill masses can be heated to a temperature which is preferably in the range between 70 and 100°C and then cooled to a temperature between 35 and 20°C, in the case of soft gelatin capsules, and 60 to 20°C in the case of hard gelatin capsules.

Preferably, the process according to the present invention comprises the subsequent steps of :

a) feeding the fill mass into a feed tank;
b) feeding the fill mass from the feed tank into a dosing pump;
c) dosing the fill mass through a heater and a cooler into an injection wedge;

d) injecting the heated and subsequently cooled fill mass of step c) from the injection wedge into the capsules.

To advantage, the fill mass undergoes heating also in the feed tank, at a temperature which is preferably between 35 and 95°C. In this way solidification of the fill mass in the dosing pump can be avoided, and complete or partial solidification of the fill mass that has occurred prior to the dosing pump can be reversed. In addition, heating of the feed tank reduces the viscosity of the fill mass and therefore reduces the risk and extent of solidification of the fill mass caused by shear stress in the dosing pump.

In accordance with a preferred embodiment of the present invention, the fill mass undergoes heating in the dosing pump, at a temperature which is preferably between 35 and 80°C. The heating of the dosing pump, e.g. electrically, avoids solidification of the fill mass in the dosing pump or reverses solidification of the fill mass that has occurred prior to the dosing pump. As the contact time of the fill mass in the dosing pump is short, heating of the latter is also suitable for thermolabile substances.

In a particularly preferred embodiment of the present invention, the fill mass is heated in the feed tank, as well as in the heating pump, preferably at the above temperatures.

By using the process of the present invention, capsules are obtained wherein the fill mass remains highly homogeneous for at least six to twelve, or even 24 months after production. These capsules have a constant dissolution rate of at least 70% of the drug substance within 30 minutes after administration.

The present invention relates also to soft and hard gelatin capsules containing a shear sensitive fill mass and having a constant dissolution rate of at least 70% of the drug substance within 30 minutes after administration, obtainable by the process in accordance with the present invention. The fill mass of such capsules preferably contains, as active ingredient, a HIV protease inhibitor and, more preferably, a solution of saquinavir.

By way of example, a preferred embodiment of the present invention will now be described with reference to the accompanying figures in which:

Figure 1a is a flow sheet diagram depicting the process according to the invention for manufacturing soft gelatin capsules;

Figure 1b is a flow sheet diagram depicting the process according to the invention for manufacturing hard gelatin capsules;

Figure 2 is a rheogramm of the shear stress (Pa) over the shear rate (1/s) of three saquinavir soft gelatin capsules manufactured with the process of the invention;

Figure 3 is a rheogramm of the shear stress (Pa) over the shear rate (1/s) of a saquinavir soft gelatin capsule (C1) manufactured with the process of the invention, and of two saquinavir soft gelatin capsules (C2, C3) obtained with the conventional process;

Figure 4 is the dissolution profile of three saquinavir soft gelatin capsules manufactured with the process of the invention;

Figure 5 is the dissolution profile of a saquinavir soft gelatin capsule (C1) manufactured with the process of the invention, and of two saquinavir soft gelatin capsules (C2, C3) obtained with the conventional process.

Referring now to figures 1a and 1b, the fill mass is prepared in a mixing vessel 1, wherein the active agent is dissolved, emulsified or suspended in an appropriate solvent, eventually together with antioxidants and/or other additives. The so obtained solution, emulsion or suspension, is transferred into a storage tank 2, and then pumped into a feed tank 3 heated by a water bath. From the feed tank 3, the fill mass is fed by gravity to an electrically heated dosing pump 4 controlling the flow of the mass which will be injected in the gelatin capsules. The fill mass flowing out from the dosing pump 4 undergoes heating in a heating bath 5 (oil or water) and afterwards cooling in a cooling bath 6 (cold water) and is finally fed to a filling wedge 7 for injection into the gelatin capsule.

For the manufacture of soft gelatin capsules (figure 1a), gelatin mass is fed by gravity to a metering device 8 which controls the flow of the mass onto rotating drums (not shown). Gelatin ribbons 9 of controlled thickness are thus formed. The ribbons 9 are fed through a lubricant bath (not shown), over guide rolls (not shown) and then down between the wedge 7 and die rolls 10.

The fill mass is dosed, through orifices (not shown) of the wedge 7 into the gelatin ribbons 9 between the die rolls 10, wherein the orifices are lined up with die pockets 11 of the die rolls 10. The capsule is about half sealed when the pressure of the pumped fill mass forces

the gelatin into the die pockets 11, where the capsules are simultaneously filled, shaped, hermetically sealed and cut from the gelatin ribbons 9. The sealing of the capsule is achieved by mechanical pressure on the die rolls 10 and by heating of the gelatin ribbons 9 by the wedge 7.

For the manufacture of hard gelatin capsules (fig. 1b), the fill mass is dosed through orifices (not shown) of the wedge 7 into previously prepared hard gelatin shells.

Example

Saquinavir gelatin capsules having the composition listed in Table 1 were prepared according to the process already described.

Table 1a: Composition of saquinavir gelatin capsule

Ingredient	**mg/Capsule**
Capsule Fill:	
Saquinavir (amorphous)	200.00
Medium Chain Mono and Diglycerides	765.00
Povidone K 30	30.00
DL-alpha-Tocopherol	5.00
Mass of capsule contents	1000.00
Capsule Shell:	
Gelatin	250.92
Glycerol 85%	168.73
Titanium Dioxide	3.06
Yellow Iron Oxide	0.20
Red Iron Oxide	0.027
Mass of capsule shell	422.937

Table 1b: Composition of saquinavir hard gelatin capsule

Ingredient	mg/Capsule
Capsule Fill:	
Saquinavir (amorphous)	120.00
Medium Chain Mono and Diglycerides	459.00
Povidone K 30	18.00
DL-alpha-Tocopherol	3.00
Mass of capsule contents	600.00
Capsule Shell:	
Gelatin	96.00

Table 2: Temperature profile in the different plant units

Plant unit	Temperature profile
Mixing vessel 1 (under stirring)	75-105 min at 63°C
	5 min at 83°C
	cooling at 28°C
Storage tank 2	25°C
Feed tank 3 (in water bath)	50°C (bath)
	35-40°C (fill mass)
Dosing pump 4	50°C (pump)
	40°C (fill mass)
Heating bath 5	90°C (bath)
	from 40°C to 90°C within 2 min (fill mass)
Cooling bath 6	20°C (bath)
	from 90 to 30-25°C (fill mass)
Filling wedge 7	25°C (fill mass)

The optical density and the light scattering of the capsule content (C) obtained with the process according to the invention were measured. Table 3 shows the values of the content (C) of three soft gelatin capsules obtained with the process of the invention and of the

content of three soft gelatin capsules obtained with a conventional process (i.e. without heating in the feed tank, in and after the dosing pump).

Table 3: Optical Density (540 nm, 5x5 mm cell) and Light Scattering (500/500 nm, 5x5 mm cell).

	Conventional Process			**Process according to the invention**		
	C 1	C 2	C 3	C 1	C 2	C 3
Optical Density	0.862	1.391	0.343	0.010	0.014	0.008
Light Scattering	34.3	23.8	23.8	0.010	0.010	0.000

As shown in Table 3, the optical density and the light scattering values of the capsule content produced according to the above process are much lower than those obtained with conventional processes and, above all, they are highly reproducible.

In figures 2 and 3 it can moreover be seen that the fill masses of the capsules obtained with the above process are always Newtonian liquids (fig. 2, straight lines) while those of capsules manufactured with conventional processes never show such a behaviour (fig. 3, C2, C3).

The capsules obtained with the above process are therefore much more superior in their homogeneity and limpidity than those obtained with conventional processes.

The saquinavir gelatin capsules obtained with the above process strongly improve their dissolution rate, if compared with conventional capsules, as clearly depicted in figure 5, wherein C1 is a capsule according to the invention and C2, C3 are two capsules made with the conventional technique. The dissolution rate of the present saquinavir gelatin capsules is moreover well reproducible, as clearly shown in figure 4.

Claims

1. A process for encapsulating a shear sensitive fill mass into a capsule, characterised in that said fill mass is heated and subsequently cooled, immediately prior to the encapsulation.

2. The process according to claim 1, wherein the capsule is a soft gelatin capsule.

3. The process according to claim 2, wherein the fill mass is heated at a temperature between 0 and 20°C above its melting point, and subsequently cooled at a temperature between 35 and 20°C.

4. The process according to claim 1, wherein the capsule is a hard gelatin capsule.

5. The process according to claim 4, wherein the fill mass is heated at a temperature between 0 and 20°C above its melting point, and subsequently cooled at a temperature between 60 and 20°C.

6. The process according to claim 3 or claim 5, wherein the fill mass comprises, as an active ingredient, a HIV protease inhibitor which undergoes the heating at a temperature between 70 and 100°C.

7. The process according to claim 6, wherein the fill mass is a solution of saquinavir.

8. The process according to any preceding claims, comprising the subsequent steps of:
   a) feeding the fill mass into a feed tank (3);
   b) feeding the fill mass from the feed tank (3) into a dosing pump (4);
   c) dosing the fill mass through a heater (5) and a cooler (6) into an injection wedge (7);
   d) injecting the heated and subsequently cooled fill mass of step c) from the injection wedge (7) into the capsules.

9. The process according to claim 8, wherein the fill mass undergoes heating in the feed tank (3).

10. The process according to claim 9, wherein the fill mass is heated at a temperature between 35 and 95°C.

11. The process according to any one of claims 8, 9, 10, wherein the fill mass undergoes heating in the dosing pump (4).

12. The process according to claim 11, wherein the fill mass is heated at a temperature between 35 and 80°C.

13. A soft or hard gelatin capsule containing a shear sensitive fill mass and having a constant dissolution rate of at least 70% of the drug substance within 30 minutes after administration, obtainable with the process according to any one of claims 1 to 12.

14. The invention as hereinbefore described.

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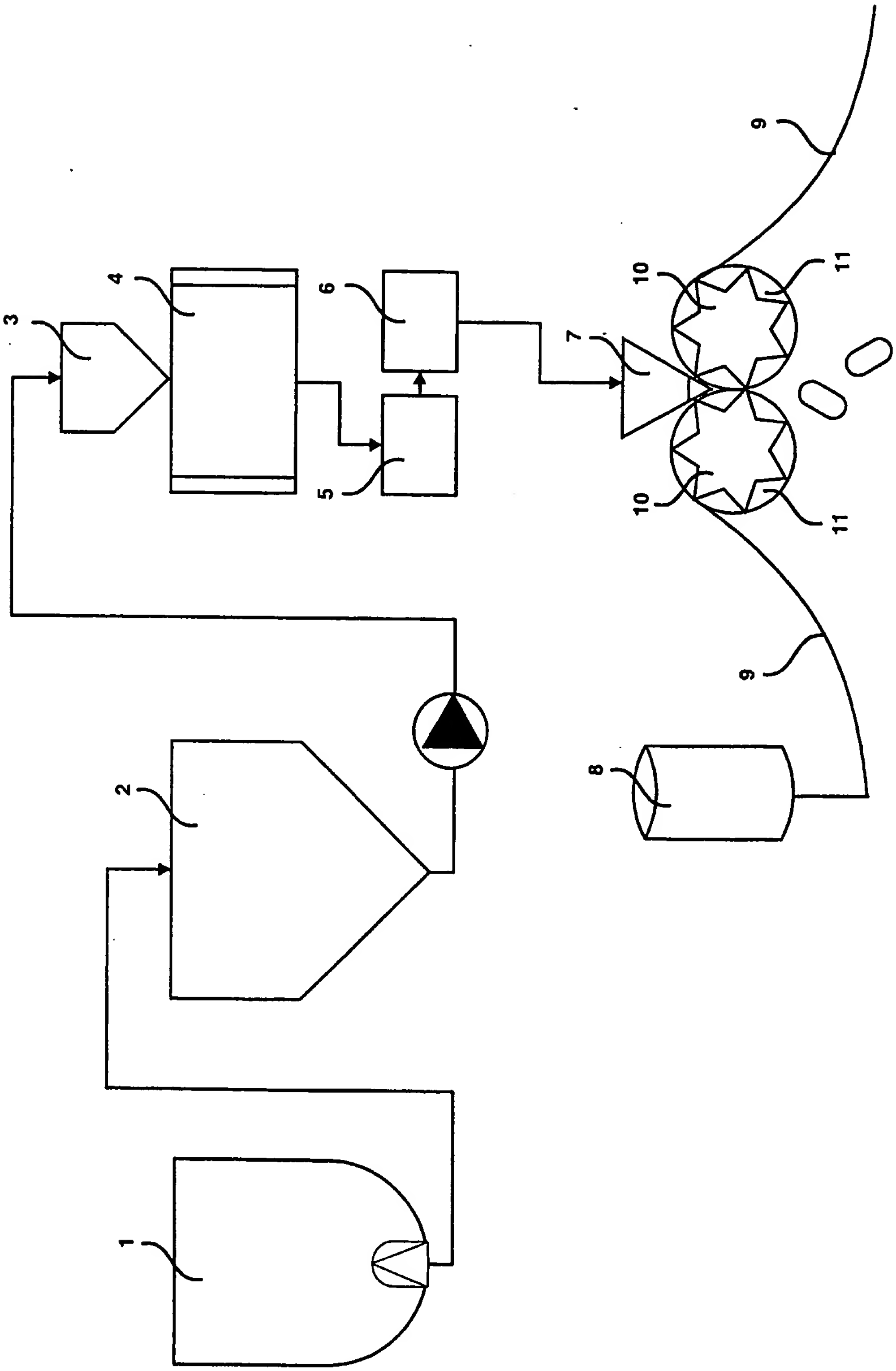


Fig. 1 a

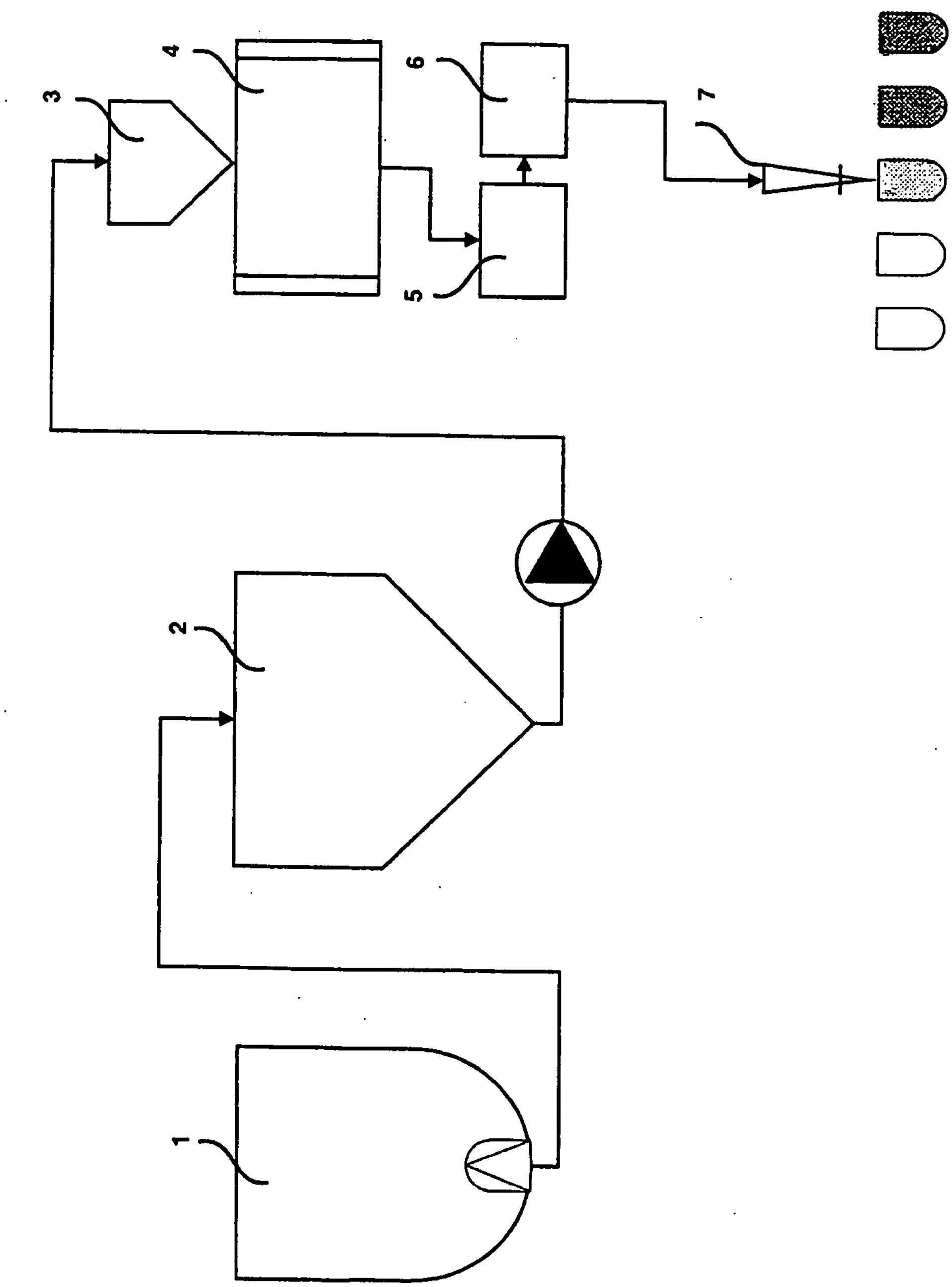
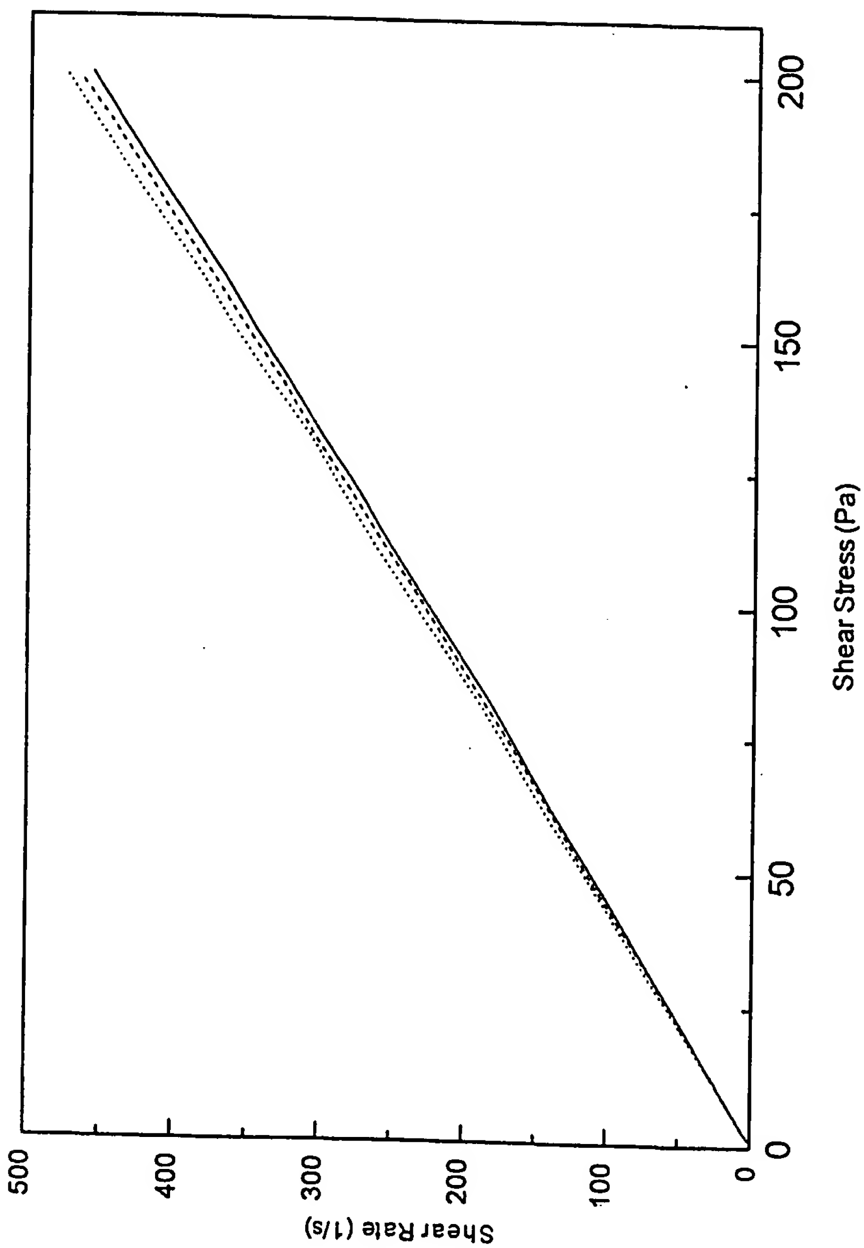


Fig. 1 b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300
400
500
Shear Stress (Pa)
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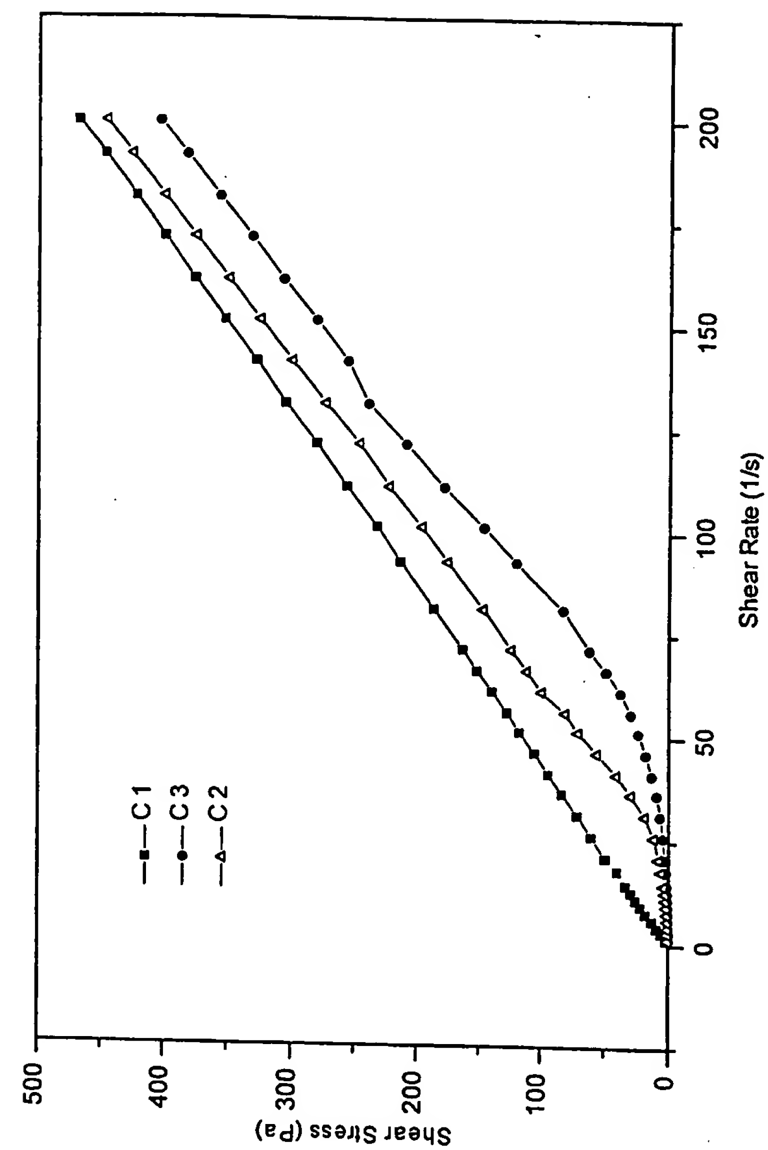
50
100
150
200

Fig. 2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C 3
C 2
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Shear Stress (Pa)
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50
100
150
200
100
200
300
400
500

Fig. 3

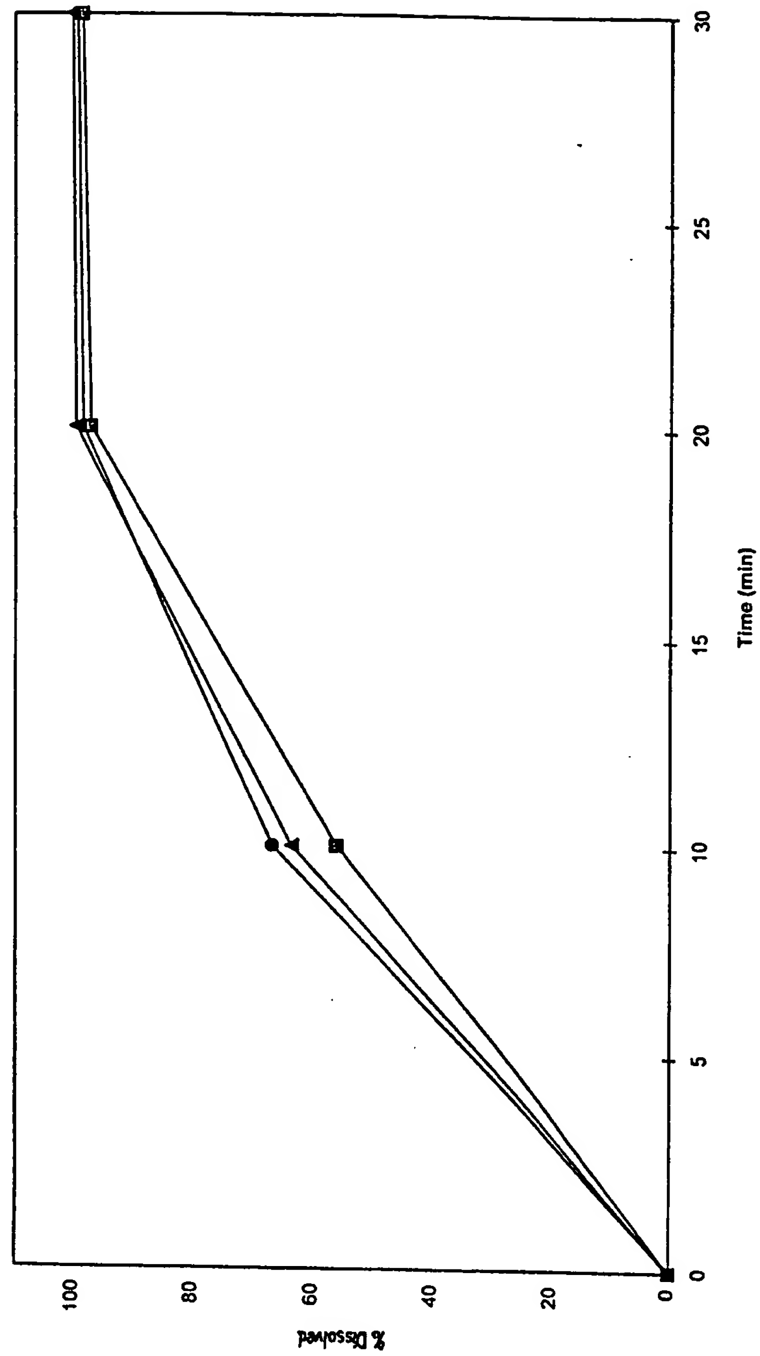

Fig. 4

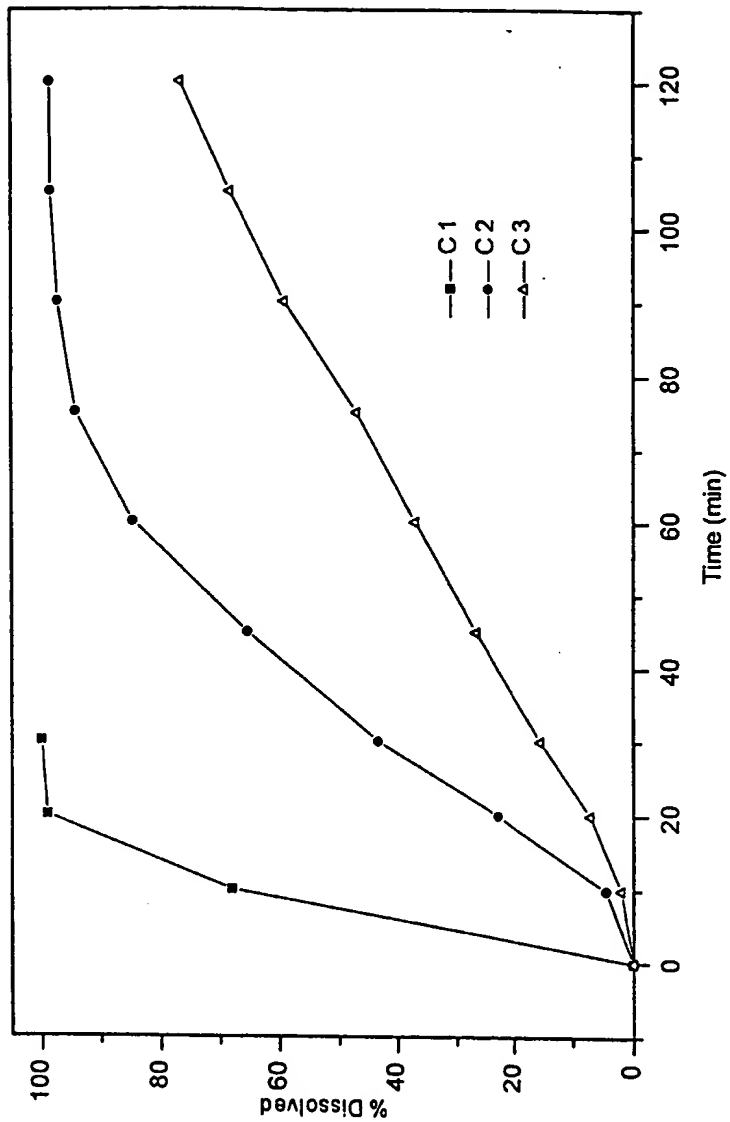

Fig. 5

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 99/08684

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J3/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61J A61K B65B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 85 36 337 U (R.P.SCHERER) 13 February 1986 (1986-02-13) claim 1; figure 1	1,2,8,13
A	EP 0 040 840 A (NIPPON ELANCO) 2 December 1981 (1981-12-02) page 3, line 6 -page 4, column 6; figure 1	1,8,13
A	US 2 692 404 A (PLOURDE) 26 October 1954 (1954-10-26) column 1, line 1 - line 31 column 5, line 59 -column 6, line 38; figure 1	1,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2000	24/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baert, F

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Information on patent family members

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PCT/EP 99/08684

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